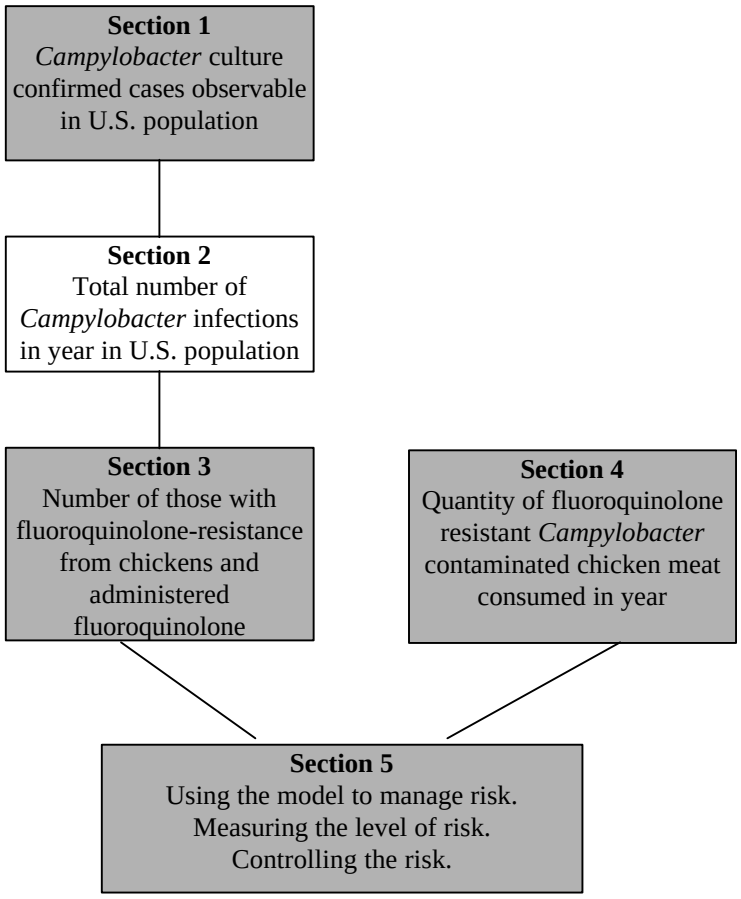
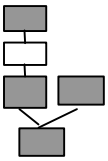
Section 2

Estimate of the total number of human campylobacteriosis cases in the U.S. in a specified year





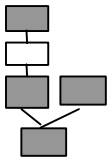
Symbol	Description	Formula
p_{bm}	Proportion of *Campylobacter* bloody diarrhea enteric infections seeking medical care	Beta distribution based on data
p_{nm}	Proportion of *Campylobacter* non-bloody diarrhea enteric infections seeking medical care	Beta distribution based on data
p_{bc}	Proportion of enteric bloody diarrhea infections seeking care who are requested to supply stool sample and comply	Composite distribution based on data
p_{nc}	Proportion of enteric non-bloody diarrhea infections seeking care who are requested to supply stool sample and comply	Beta distribution based on data
p_t	Proportion of submitted stool specimens that are tested by the laboratory	Beta distribution based on data
p_+	Proportion of infected stool specimens that test positive	Beta distribution based on data
$N2_i$	Estimate of expected number of people in U.S. population ill with invasive disease *Campylobacter* in year	$=N1_i$
$N2_{eb}$	Estimate of expected number of people in U.S. population ill with enteric *Campylobacter* infection and bloody diarrhea in year	$=N1_{eb}/(p_{bm}*p_{bc}*p_t*p_+)$
$N2_{en}$	Estimate of expected number of people in U.S. population ill with enteric *Campylobacter* infection and non-bloody diarrhea in year	$=N1_{en}/(p_{nm}*p_{nc}*p_t*p_+)$
$N2_T$	Estimate of expected total number of people in U.S. population with *Campylobacter* infection	$=N2_i+N2_{eb}+N2_{en}$

Parameter estimations

2.1 (p_{bm}, p_{nm}) - Proportion of *Campylobacter* enteric illnesses seeking medical care

Two estimates were provided for this proportion, one for the probability that a person with enteric illness would seek care if they reported blood in their stool (p_{bm}) and one (p_{nm}) for non-bloody diarrhea.

The proportion of cases that sought care for "diarrheal illness" is based upon a 1996-7 population survey of 9,003 persons. The people interviewed were from the general population of the five original FoodNet sites (selected counties in California, Connecticut, and Georgia and the states of Minnesota and Oregon), representing 5% of the U.S. population (17, 35). The survey was conducted for the entire year. Approximately 150 persons per site were interviewed per month. People were randomly selected using a random digit dialing, single stage, Genesys-ID sampling method and were interviewed using methods similar to those used in the Behavioral Risk Factor Surveillance System. Cases excluded from the survey included persons with chronic illness, colitis, prior surgery to remove part of their stomach or intestine and irritable bowel syndrome (n=379); resulting in a total number of 8,624 usable interviews. Of the 8,624 usable interviews, **483** individuals reported having a "diarrheal illness," defined as three or more loose stools within a 24-hour period, or diarrhea lasting for more than one day or which resulted in an inability to perform normal activities and reported no visible blood in their diarrhea. Of those 483 cases with a diarrheal illness and non-bloody stools, **12%**, a weighted estimate (59/483), sought care (97). The estimate was adjusted to account for unequal probabilities of selection to allow population estimates to be made. Factors that affected selection probabilities included the number of people in a household, and number of phone lines in a house. Age and sex were also weighted, creating an "external weight" so that the sample population resembled that of the U. S.



Non-bloody Diarrhea (p_{nm})
Because a confidence interval was not available for the estimate, uncertainty about the parameter was modeled using a Beta distribution as follows:

p_{nm} = Beta(483*0.12+1, 483*(1-0.12)+1)

Although this gives a confidence interval estimate that should be quite reasonable with a large sample size, it will nevertheless underestimate the parameter uncertainty to some degree.

Bloody Diarrhea (p_{bm})
The same population survey identified **4** people who reported bloody diarrhea. Of the four persons with bloody diarrhea, two sought care and an adjusted estimate of **15%** for p_{bm} was given (97). Uncertainty about the parameter was modeled using a Beta distribution as follows:

p_{bm} = Beta(4*0.15+1, 4*(1-0.15)+1)

This distribution has a very wide spread with a mean of 26.7%.

Invasive Disease
No information is available to estimate this parameter, see Section 1.3. It was assumed that, due to the severity of illness, 100% of people with invasive *Campylobacter* illness sought care.

DISCUSSION: These estimates are for diarrheal illness, and not campylobacteriosis specifically. Data for campylobacteriosis specifically was not available. Bacterial foodborne disease is typically more severe than viral foodborne disease (28) and rates of seeking care may differ by pathogen.

In the population survey, factors that were most important in influencing the decision to seek care were fever, vomiting, "how sick they felt," stomach cramps, reporting blood in stool and duration of diarrhea (35). Some of these factors were evaluated for diarrheal illness in the telephone survey and compared with the same characteristics in individuals who had culture-confirmed *Campylobacter* infections or diarrheal disease (Table 2.1). Comparing the groups, a greater proportion of people with culture-confirmed *Campylobacter* cases were affected by fever and blood in the stool than the people seeking care for diarrheal illness. Therefore, the actual rate of seeking care for campylobacteriosis may be underestimated by the 12% overall rate (12% non-bloody and 26.7% bloody stools). However, because a greater proportion of people with fever and bloody stools would be cultured and enrolled in the case control study, such comparisons are difficult.

ASSUMPTION(s): The rate at which people reporting bloody stools seek care is similar to the rate at which people with campylobacteriosis reporting bloody stools seek care. The rate at which people with non-bloody stools seek care for diarrheal illness is similar to the rate at which people with campylobacteriosis reporting non-bloody stools seek care.

DATA GAP: Additional studies to define the rate at which people with campylobacteriosis seek care would be helpful and would provide a more accurate estimate. These data would require very large community-based surveys that are likely to require considerable resources to conduct.

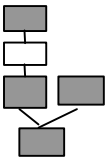


Table 2.1. Comparison of characteristics of illness most important in seeking care between the telephone population survey of all diarrheal illness (35) and culture confirmed campylobacteriosis and a survey of diarrheal disease

Characteristic	Diarrheal Illness Seeking Care & Submitted Cultures – 1997[a]	Culture-confirmed *Campylobacter* Cases 1998[b] (CCCC)	CCCC 1980-1[c]
Sample size	16	1461	239
Fever	32%	83%	74%
Vomiting	26%	30%	38%
Stomach Cramps	68%	86%	79%
Blood in stool	6%	46%	46%

[a]Population Survey,(Ref. 1, Table 3)
[b]*Campylobacter* Case Control Study (Ref. 97)
[c]Survey conducted in eight hospitals in the National Nosocomial Infections Study (Ref. 14, Table 2).

2.2 (p_{bc}, p_{nc}) - Proportion of enteric bloody and non-bloody diarrhea infections seeking care who are requested to supply stool sample and comply

Two estimates were provided for this proportion, equivalent to the probability that a person with an enteric illness would be requested to submit a stool sample and comply, if they reported visible blood (p_{bc}) or not (p_{nc}) in their stool.

The probability that a specimen was requested and submitted was determined from the same population survey of the five FoodNet sites as listed in Section 2.1 for non-bloody diarrhea. For bloody diarrhea, the sample size in the population survey was not sufficiently large to provide an estimate and a survey of physicians estimating the frequency of their requests for a specimen was used instead (34, 91). The physicians' survey was conducted in 1996, based upon a stratified random mail survey of 2,939 (58%) physicians returning surveys out of 5074 mailed, from the FoodNet catchment area. Data was collected on the physician's practice, and the characteristics of the last patient with diarrhea seen by the physician. Data from 1,752 practitioners that saw patients for more than 8 hours per week were analyzed (34).

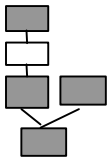
Non-Bloody Diarrhea (p_{nc})
From the CDC population survey that identified **59** people reporting non-bloody diarrhea that were requested to submit and did submit a stool sample for culture, CDC provided an adjusted estimate of **18.1%** for p_{nc}. The unweighted estimate was 14/59 or 23.7% (97). The estimate was adjusted to account for the number of people in a household, number of phone lines in a house, see Section 2.1.

Confidence intervals were not available with the weighted estimates and in the absence of confidence intervals, uncertainty about the parameter was modelled using a Beta distribution as follows:

p_{nc} = Beta(59*0.181+1, 59*(1-0.181)+1)

Again, although this gives a confidence interval estimate that should be quite reasonable when we have a large sample size, it will nevertheless underestimate the parameter uncertainty because we have implicitly evened out the uncertainty over all of the weighted categories.

Bloody Diarrhea (p_{bc})
In the population survey, the proportion of persons with a diarrheal illness that reported blood in their stools were requested to submit a stool sample and did submit was 100% (adjusted estimate based on 2/2)(97). The rate of seeking care and the rate of ordering cultures are thought to be higher among cases reporting bloody diarrhea than they are among cases reporting non-bloody diarrhea. However, there were only 4 cases identified as having bloody diarrhea in the telephone survey so this hypothesis could not be



confirmed. Two of the four sought care and both were requested and did submit cultures. While these results are consistent with the hypothesis that persons reporting bloody diarrhea are more likely to seek care and submit samples, the sample is not large enough to reach that conclusion.

In the physician survey 78% (**14**/**18**) of the 18 physicians reported requesting a bacterial stool culture from a patient with a bloody stool (34)[1]. Factors significantly associated with stool culture requests as determined from multivariable logistic regression were the presence of bloody stools, diagnosis of AIDS, diarrhea longer than three days, travel to developing countries and fever.

The physician's survey responses indicated that physicians report a higher rate of requesting cultures for persons with non-bloody stools (40%) (34), than the population survey rate of patients reporting being requested to submit a specimen (18.1%) (35). The sample size in the population survey was not sufficiently large to provide a reliable estimate of the rate of being requested to submit and complying for cases with observable blood in the stool. A uniform distribution was used to model this parameter in recognition of the small amount and conflicting nature of the available data. The upper limit of the uniform distribution was the proportion of patients with observable blood in their stools from whom physicians reported requesting samples, 79%. The lower bound of the uniform distribution adjusts for possible physician over-reporting. The adjustment used reduces the estimated proportion by multiplying the upper bound by the ratio of patient to doctor reporting of stool sample requests among cases with non-bloody stools (18.1%/40% is the point estimate of the ratio). In the confidence distribution, 18.1% was replaced by its modelled value p_{nc}. It was assumed that 100% of persons reporting observable blood in their diarrhea who were asked to submit a stool specimen would have complied. Thus, the proportion of persons reporting observable blood in their diarrhea, who were requested to submit and complied, is the same as the proportion of persons who were requested to submit.

In summary, p_{bc} was modelled with a Uniform((p_{nc}/0.40)*x), x) confidence distribution, where x = Beta(14+1, 18-14+1).

Invasive Disease

There is no information on the rate of physician requests for diagnostic testing or rate of sample submission for cases of invasive disease caused by *Campylobacter*, see Section 1.3. In this assessment, we have assumed a rate of 100%.

ASSUMPTION: The probability that a stool specimen was requested among people with diarrheal illness reporting bloody stools is similar to the probability that a stool specimen was requested among people with campylobacteriosis reporting bloody stools. The probability that a stool specimen was requested among people with diarrheal illness reporting non-bloody stools is similar to the probability that a stool specimen was requested among people with campylobacteriosis reporting non-bloody stools.

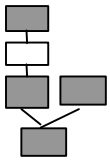
ASSUMPTION: Over-reporting by physicians of the proportion of persons with bloody diarrhea that are requested to submit stool specimens, compared to the proportion of stool requests reported from the persons with bloody diarrhea, is similar to physician over-reporting for persons without observable blood in their stools.

2.3 (p_t) - Proportion of submitted stool specimens that are tested for *Campylobacter* by the laboratory

Non-Bloody Stool and Bloody Stool

In a survey of 309 laboratories in the five original FoodNet sites (CA, CT, GA, MN, OR, population 14,281,096 million persons), **389,255** stools were submitted during 1996. In the laboratories surveyed,

[1] Further study of this work has shown that there are more data points than we have used here. The larger data set will be used in the final report. It will have little impact on the results except to slightly decrease model output uncertainty.



367, 846 (94.5%) of submitted stool specimens were tested for *Campylobacter* (89). This laboratory survey will be repeated in 1999.

Thus, this parameter was modelled using a Beta(367846+1, 389255-367846+1) distribution which is essentially a single point estimate of 94.5% because of the very large data set.

Invasive Disease
No information is available for an estimate, see Section 1.3. The proportion is assumed to be 100% for invasive disease.

2.4 (p_+) - Proportion of infected stool specimens that test positive if the organism is present, test sensitivity

The problems with the lack of sensitivity of stool culture are two-fold. First, stool culture techniques lack sensitivity as *Campylobacter* are fastidious microaerophillic organisms that, when exposed to oxygen or other stress, may enter a non-culturable state. Secondly, sensitivity of stool culture is limited by the amount of *Campylobacter* present in the stool. Finally, handling of the specimen is important and contributes to the lack of sensitivity of culture of *Campylobacter*. Sub-optimal specimen handling and storage may allow competitive growth by other bacteria or result in low numbers of *Campylobacter* in the stool that could reduce the likelihood that *Campylobacter* will be identified during culture. In addition, there are no standardized methods for isolation of *Campylobacter* and the increased costs associated with enrichment procedures and utilization of highly selective media that would improve isolation discourages their routine use.

In an outbreak at a camp in New Zealand of *Campylobacter* enteritis, in 1990, associated with exposure to spring water, of 116 persons attending or resident at the camp, 44 showed clinical symptoms. Of the 44 clinical cases, 14 showing signs of enteric disease submitted stools for culture. Of the **14** specimens submitted from clinically affected individuals only **11** (78.6%) cultured positive for *Campylobacter* (18a). Serology was not conducted to determine if rising titers of immunoglobulins were evident in persons ill and culture negative to determine if they may have been exposed to the pathogen.

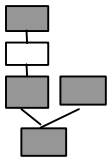
Because another, U.S. related, estimate of the sensitivity of stool culture was not available and to assess whether this estimate was a close approximation to the true value for the sensitivity of stool culture, Dr. Fred Angulo, the from CDC and Dr. Irving Nachamkin, from the University of Pennsylvania Medical Center, were surveyed for their expert opinions of the sensitivity of stool culture for *Campylobacter*. Their estimates of 70% and 75%, respectively were close to the mean value of the parameter modelled.

DISCUSSION: There is little information on the sensitivity of stool culture methods and the methods for culturing stools are extremely diverse. Specimen handling is another factor that can greatly decrease the sensitivity of stool culture methods. In a review of non-typhoidal salmonellosis, an assumed estimate of the sensitivity of culturing *Salmonella* was 70% and was used to estimate the burden of salmonellosis in the U. S. (91). This estimate was adopted for determining the burden of campylobacteriosis in a recent review of foodborne disease (51).

DATA GAP: Incomplete knowledge of the sensitivity of culturing specimens for *Campylobacter* exists and an estimate with a large degree of uncertainty was used from the literature. A study to estimate the sensitivity of stool culture as commonly practiced in labs testing stool for *Campylobacter* would provide a more precise estimate.

Thus, this parameter was modelled using a Beta (11+1,14-11+1) distribution.

2.5 ($N2_{eb}$, $N2_{en}$, $N2_i$) - Estimate of expected number of people in U.S. population ill with enteric *Campylobacter* infection and bloody and non-bloody diarrhea and with invasive disease *Campylobacter* in year in population



Calculation of the estimate of illness caused by *Campylobacter* in the U.S. population is done by combining the results determined by category of disease, enteric without observable blood in stools, enteric with observable bloody stools and invasive disease.

($N2_{eb}$, $N2_{en}$): The estimates of illness caused by *Campylobacter* in the U.S. population by category of disease, enteric with observable bloody stools and enteric without observable blood in stools are calculated as follows:

$N2_{eb} = N1_{eb}/(p_{bm}*p_{bc}*p_t*p_+)$
$N2_{en} = N1_{en}/(p_{nm}*p_{nc}*p_t*p_+)$

($N2_i$): The estimate of expected number of people in U.S. population ill with invasive disease caused by *Campylobacter* in a year is determined as equal to $N1_i$. This assumes that, due to the severity of the illness, all invasive cases of campylobacteriosis would seek care and provide a stool sample.

Section 2 Summary

The expected total number of cases of campylobacteriosis is then estimated as $N2_T = N2_i + N2_{en} + N2_{eb.}$ The estimate for 1998 using this model is given in Figures 2.1a and Figure 2.1b. It shows that we are 90% confident that the true value lies between 1.3 and 4.3 million. The mean value of the distribution is 2.48 million cases and the median is 2.16 million cases. Relative contributions of the various components of the model to the model uncertainty will be presented in Section 5, Sensitivity Analysis.

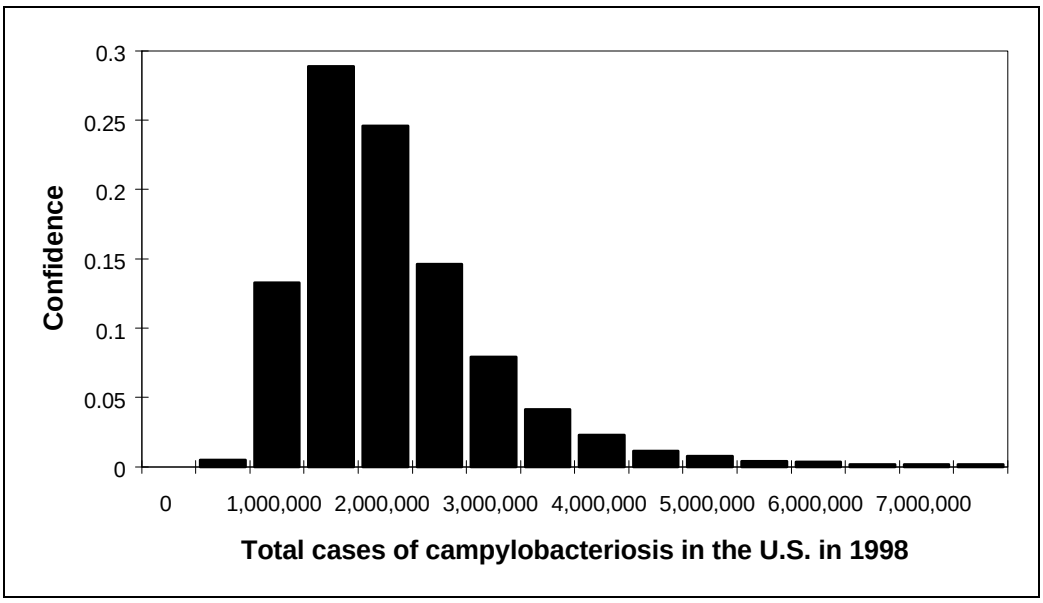


Figure 2.1a. The confidence distribution (distribution of uncertainty) for the total number of cases of campylobacteriosis in the U.S. for 1998.

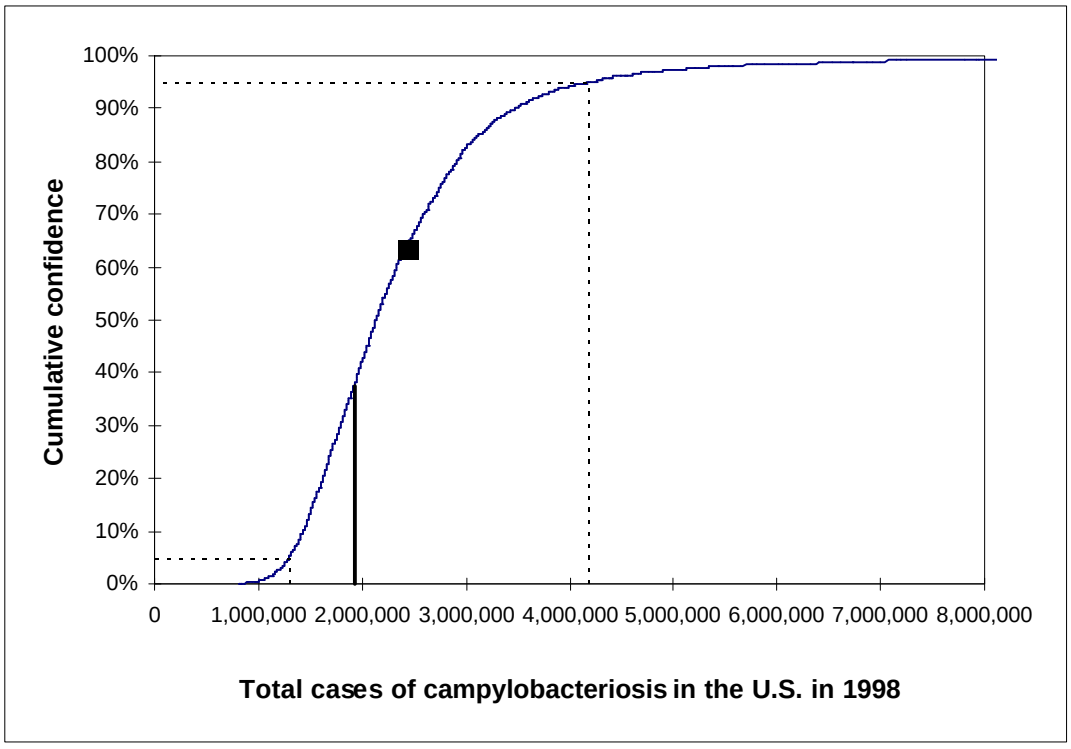


Figure 2.1b. The cumulative confidence distribution for the total number of cases of campylobacteriosis in the U.S. for 1998. The solid vertical line shows the CDC's estimate for 1998.